Original Article

Olmesartan Reducing Incidence of Endstage Renal Disease in Diabetic Nephropathy Trial (ORIENT): Rationale and Study Design

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Diabetic nephropathy (DN) is a leading cause of endstage renal disease (ESRD) in Japan and Hong Kong. Asian patients are known to be more predisposed to DN and ESRD than Caucasians. Strict blood glucose and blood pressure control are key factors in prevention and treatment of DN. In the last decade, inhibition of the renin-angiotensin-aldosterone (RAA) system has been confirmed to reduce the incidence of cardiovascular complications in Caucasian patients with diabetes. Although the RENAAL study has demonstrated the beneficial effects of inhibition of the RAA system on prevention of ESRD and death in type 2 diabetic patients with overt proteinuria, only 17% of patients in this multicenter study were of Asian ethnicity. Given the predilection of Asian diabetic patients for renal complications and the rising burden of ESRD, there is a need to confirm these findings in a homogenous group of Asian patients. The ORIENT (Olmesartan Reducing Incidence of Endstage Renal Disease in Diabetic Nephropathy Trial) is a randomized, double-blind, placebo-controlled study in Japan and Hong Kong to evaluate the renal protective benefits of olmesartan medoxomil in type 2 diabetic patients with overt proteinuria (urinary albumin to creatinine ratio ≥300 mg/g creatinine) and renal insufficiency (serum creatinine: 1.0–2.5 mg/dl). The study has a targeted enrollment of 400 Japanese and Hong Kong Chinese patients. The primary outcome is the composite endpoint of time to the first occurrence of doubling of serum creatinine, ESRD (serum creatinine more than 5.0 mg/dl, the need for chronic dialysis, or renal transplantation) or death. The average follow-up period is 4 years and the study ends in 2009. (*Hypertens Res* 2006; 29: 703–709)

***Key Words*: angiotensin II receptor blocker, diabetic nephropathy, endstage renal disease, type 2 diabetes, olmesartan medoxomil**

Introduction

The population of diabetic patients is growing significantly worldwide, and its high prevalence in Asia, including in Japan and Hong Kong, is a matter of great concern in light of the increasing number of patients with severe diabetic complications such as blindness, leg amputation and renal death, and the associated medical expenditures.

Diabetic nephropathy (DN), one of the major complications of diabetes mellitus, is a progressive renal microangiopathy characterized by mesangial expansion and nodular sclerosis

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Received April 21, 2006; Accepted in revised form June 16, 2006.

due to chronic hyperglycemia. It develops with clinical manifestations such as proteinuria, hypertension and edema, and culminates in renal failure.

As the prevalence of diabetes increases, the number of new renal dialysis patients is expected to continue to rise in Asia, including in Japan and Hong Kong (*1–3*). Along with the growing concerns about escalating medical costs and the increased risk of cardiovascular disease caused by chronic kidney disease (*4*, *5*), interruption of the development of DN and slowing the progression of endstage renal disease (ESRD) have become urgent issues.

In order to interrupt the development of DN, it is critical to manage blood glucose, hypertension and proteinuria aggressively (*6–9*). In recent years, large-scale clinical trials conducted in type 2 diabetic patients with nephropathy, such as the RENAAL study of losartan (*10*), the IDNT study of irbesartan (*11*), and the IRMA-2 study (*12*), have shown that angiotensin II (AII) receptor blockers (ARB) can slow the progression of DN (*10–15*). Treatment with an ARB significantly reduces the risk of doubling of the serum creatinine level, dialysis, renal transplantation, and death in addition to protecting against the development of microalbuminuria into overt proteinuria.

There have been studies suggesting that Asian patients with diabetes are more predisposed to develop nephropathy than their Caucasian counterparts (*16*, *17*). In a subgroup analysis of the RENAAL study, ARB therapy was found to be more effective in Asian than Caucasian patients in delaying the progression of DN (*18*). In order to examine more closely the effects of ARB treatment in Asian patients on the inhibition of progression of DN, we are conducting a large-scale clinical trial named ORIENT (Olmesartan Reducing Incidence of Endstage Renal Disease in Diabetic Nephropathy Trial). This is a randomized, double-blind, placebo-controlled, multinational study to evaluate the renal protective benefits of olmesartan medoxomil using the composite clinical endpoint of time to the first occurrence of doubling of serum creatinine, ESRD, or death.

Method

Subjects

The ORIENT is a multinational, multi-center study currently underway in Japan and Hong Kong. A total of 400 Japanese and Hong Kong Chinese patients with type 2 DN met the inclusion and exclusion criteria shown in Table 1 and have been enrolled. In this clinical trial, DN patients are defined as those who meet at least one of the following entry criteria: 1) patients who have been diagnosed with DN by renal biopsy; 2) patients with diabetic retinopathy or diabetic neuropathy; and 3) patients with duration of type 2 diabetes of more than 5 years. The trial is being conducted under the Helsinki Declaration, and was approved by the Institutional Review Board at each trial site. All participants have been fully informed by the investigators and gave their informed consent.

Table 1. Eligibility Criteria

Inclusion criteria
1) Patients with diabetic nephropathy (DN) associated with type 2 diabetes
2) Patients aged 30 to 70 years
3) Outpatients
4) Urinary albumin to creatinine ratio: ≥300 mg/g creatinine in the first morning urine sample
5) Serum creatinine level: 1.0–2.5 mg/dl in women and 1.2–2.5 mg/dl in men
Exclusion criteria
1) Type 1 diabetes or non-DN
2) History of myocardial infarction (MI) or coronary artery bypass grafting (CABG) within 3 months prior to consent acquisition
3) History of percutaneous coronary intervention (PCI), carotid artery or peripheral artery revascularization within 6 months prior to consent acquisition
4) Stroke or transient ischemic attack (TIA) within the last 1 year
5) Unstable angina pectoris
6) Heart failure of New York Heart Association (NYHA) functional class III or IV
7) Rapid progression of renal disease within 3 months prior to consent acquisition
8) Severe orthostatic hypotension
9) Serum potassium level: ≤3.5 mEq (mmol)/l or ≥5.5 mEq (mmol)/l

Study Design

This clinical trial is a randomized, double-blind, placebo-controlled study (Fig. 1).

Screening Period

During the 6-week screening period (already completed) patients were assessed for inclusion and exclusion criteria for eligibility for entry to this trial.

Active Treatment Period

To achieve an average follow-up period of 4 years, the active treatment period is 240 weeks (5 years), taking into account the likely enrollment period of 2 years.

According to the Japanese Society of Hypertension guidelines (JSH 2000) for the management of hypertension (*19*), the target blood-pressure should be <130 mmHg systolic blood pressure and <85 mmHg diastolic blood pressure (seated blood pressure) in both diabetic patients and hypertensive patients with renal disease. In ORIENT, this blood pres-

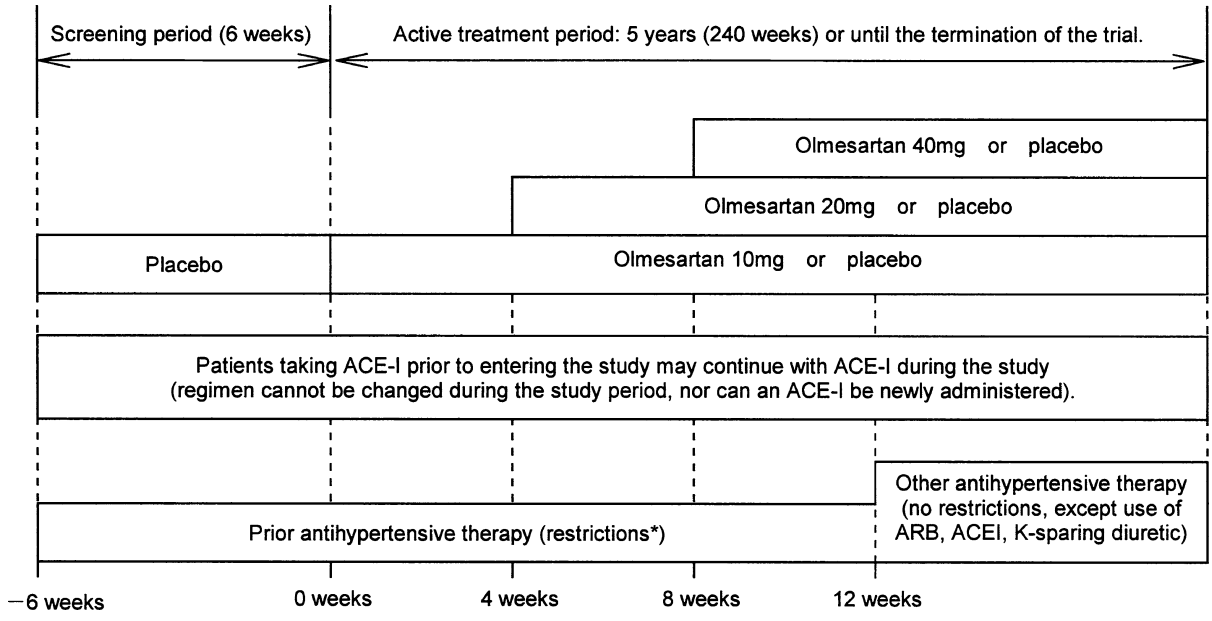

Fig. 1. *Overview of the Design of the ORIENT. *Neither an increase in dose nor administration of an additional antihypertensive drug is allowed during the screening period and the first 12 weeks of the active treatment period.*

Table 2. Primary and Secondary Outcomes

Primary outcomes
1) Efficacy: Composite endpoint of the first occurrence of any of the following events: Doubling of serum creatinine level, ESRD (serum creatinine ≥5.0 mg/dl, transplantation, dialysis), Death
2) Safety
Secondary outcomes
1) Composite endpoint of the first occurrence of any of the following events: Cardiovascular death, Non-fatal stroke except for transient ischemic attacks (TIAs), Non-fatal myocardial infarction, Hospitalization for unstable angina, Hospitalization for heart failure, Coronary/carotid/peripheral revascularization, Lower extremity amputation
2) Change in proteinuria
3) Reciprocal of serum creatinine

ESRD, endstage renal disease.

sure is used as a target level.

In the active treatment period, patients will be assigned randomly to commence treatment with either 10 mg olmesartan medoxomil (or placebo) in addition to their existing antihypertensive therapy. If the target blood pressure of less than 130/85 mmHg is not achieved after the first 4 weeks of therapy or at any time thereafter, the dose of olmesartan medoxomil (or placebo) will be increased to 20 mg daily (or placebo), with further titration to a dose of olmesartan medoxomil 40 mg daily (or placebo), if necessary.

Every reasonable attempt will be made to up-titrate the test drug to the maximum dose, even if the target blood pressure levels are achieved. However, if the target blood pressure levels are not achieved in a patient with a maximal dosage of olmesartan medoxomil, additional antihypertensive agents may be used. Except for the use of potassium-sparing diuretics, other ARBs or angiotensin-converting enzyme inhibitors (ACE-Is) not given at baseline, additional antihypertensive agents may include diuretics, β-blockers, calcium channel blockers, and α-blockers. Any patient taking an ACE-I prior to entering the study must continue with the same dose of ACE-I throughout the study. New prescription of an ACE-I after commencement of the study is not allowed.

Use of concomitant immunosuppressants, adrenocorticotropic hormones (ACTH), carbonaceous adsorbents, and any investigational drugs under development is prohibited. Chronic use of systemically administered steroids and/or nonsteroidal anti-inflammatory drugs (NSAIDs), or aspirin >330 mg/day is also prohibited.

Study Endpoints

All patients will visit the clinic at 2, 4, 8, and 12 weeks, and then return every 12 weeks throughout the study duration. At each visit, blood pressure will be measured and clinical samples collected for measurement of the urinary protein to creatinine ratio, and the levels of serum creatinine and serum potassium. All randomized patients including those discontinued from the study for any reason other than death will be followed up to collect information on primary and secondary endpoints until termination of study.

The primary and secondary outcomes are shown in Table 2. The primary efficacy endpoint of ORIENT is a composite endpoint of the time to first occurrence of doubling of serum creatinine, ESRD, or death. ESRD is defined as serum creatinine more than 5.0 mg/dl, the need for chronic dialysis, or renal transplantation. Throughout the trial, the safety and tolerability of olmesartan medoxomil will be assessed.

Secondary efficacy endpoints of ORIENT are as follows: 1) A composite endpoint of the time to first occurrence of a cerebro/cardiovascular event or cardiovascular death, non-fatal stroke except for transient ischemic attacks (TIAs), non-fatal myocardial infarction, hospitalization for unstable angina, hospitalization for heart failure, coronary/carotid/peripheral revascularization, and lower extremity amputation. 2) Change in proteinuria. 3) Reciprocal of serum creatinine.

Sample-Size Estimation

It is assumed that the primary endpoint in this study, defined as the composite renal event rate, would be 0.583 events/patient during an average 4-year follow-up period in the placebo group. The assumed event rate is calculated based on the results for Japanese patients in the RENAAL study (*18*) (event rate: 34/52=0.654 with 3.4 years average follow-up period). We assume that a 30% risk reduction would be achieved with baseline ACE-I treatment (*20*). Therefore, the event rate of the placebo group with baseline ACE-I treatment was assumed to be 0.583 with an average follow-up period of 4 years. On the other hand, the event rate of the olmesartan group with ACE-I treatment was assumed to be 0.434, since we hypothesized an additional 35% risk reduction in the olmesartan group compared to the placebo group. Based on these assumptions, 172 patients are needed in each treatment group to detect a statistically significant difference between treatment groups using the log-rank test with $\alpha=0.05$ (two-sided) and $1-\beta=0.80$. Assuming that fewer than 15% of patients will be lost to follow-up, the number of patients is determined to be 200 per group.

Statistical Analysis

The following statistical analysis plan will be applied independently for two study populations, Japanese and Chinese patients, and an integrated analysis plan for the two populations will be created including similar analysis.

Analysis Sets

All patients who have taken the study drug at least once will be included in the safety analysis set.

The primary efficacy analysis set will be the full analysis set (FAS). The FAS will include all patients satisfying the following conditions:

1) Fulfilled all entry criteria; 2) Took the study drug at least once; 3) Were followed-up at least once after randomization.

The secondary efficacy analysis set will be the per protocol set (PPS). The PPS will consist of patients included in the FAS who had no major protocol violations.

Efficacy Assessment

The Cox regression model will be used to estimate the hazard ratios with 95% confidence intervals in the renal composite event rate, the cerebro/cardiovascular composite event rate, and the event rate for each renal, cerebro- or cardiovascular event separately. The covariates included in the model will be determined based on the results of blind data review before the study is unblinded. The candidate covariates are gender, age, ACE-I treatment, baseline urinary albumin:creatinine ratio and baseline serum creatinine level. The cumulative event rate for each defined event will be estimated by the Kaplan-Meier method for each treatment group.

The linear mixed effect model, including study drugs, measurement times and other covariates selected after the blind data review, will be used for comparing the trend in the percent change in proteinuria, and the trend in the reciprocal of the serum creatinine level between treatment groups. Similar analyses for each endpoint will also be applied for the subgroup of each prognostic factor.

Safety Assessment

Adverse events will be summarized for each treatment group. The cumulative occurrence rate of all adverse events and drug-related adverse events in each treatment group will be estimated by the Kaplan-Meier method, and the log-rank test will be used to compare two groups. The summary statistics, such as the mean, median and standard deviation for the quantified laboratory test values, will be calculated at each measurement point, and scatter plots of each of the test values for pre- and post-treatment will be presented. Contingency tables showing the number of patients and the percentage of patients within each category pre- and post-treatment will also be presented for the categorical test values.

Committee

Study Coordinating Committee

The Study Coordinating Committee advises the sponsor with regard to the study design, protocol amendments, site selection, and ethical conduct of the study.

Endpoint Evaluation Committee

The Endpoint Evaluation Committee is responsible for the adjudication and classification of the primary and secondary endpoints under the blinded condition.

Independent Data Monitoring Committee

Since this trial requires follow-up of clinical events over a long period of time, the Independent Data Monitoring Committee (IDMC) monitors the trial for appropriate and ethical conduct of the study. The IDMC includes experts in the fields of nephrology, diabetes, and statistics who are independent

Table 3. Clinical Trials of ARB and ACE-I on Nephropathy in Type 2 Diabetes

Authors	Name of study (reference)	No. of patients	Maximal dose	Last BP (mmHg)	Follow-up	Results
Brenner	RENAAL (*10*)	1,513	Losartan 100 mg Placebo	140/74 142/74	3.4 years	Losartan is effective in protecting against the progression of DN
Lewis	IDNT (*11*)	1,715	Irbesartan 300 mg Amlodipine 10 mg Placebo	140/77 141/77 144/80	2.6 years	Irbesartan is effective in protecting against the progression of DN
Parving	IRMA-2 (*12*)	590	Irbesartan 300 mg Irbesartan 150 mg Placebo	141/83 143/83 144/83	24 months	Irbesartan reduced microalbuminuria
Mogensen	CALM study (*13*)	199	Lisinopril 20 mg Candesartan 16 mg Lisinopril 20 mg+ candesartan 16 mg	MR −16.7/−10.7 MR −14.1/−10.4 MR −25.3/−16.3	monotherapy 24 weeks combination 12weeks	Equivalent reduction of BP and microalbuminuria between lisinopril and candesartan monotherapy Combination therapy further decreased microalbuminuria with reduction of BP
Viberti	MARVAL (*14*)	332	Valsartan 80 mg Amlodipine 5 mg	135/78 136/79	24 weeks	Same degree of BP reduction Valsartan significantly reduced albuminuria
Barnett	DETAIL (*15*)	250	Enalapril 20 mg Telmisartan 80 mg	MR (SBP) −2.9 MR (SBP) −6.9	5 years	Equivalent renal protection

ARB, angiotensin II receptor blocker; ACE-I, angiotensin-converting enzyme inhibitor; BP, blood pressure; SBP, systolic blood pressure; MR, mean blood pressure reduction; DN, diabetic nephropathy.

from any of the study investigators and sponsor.

Discussion

The rationale of ORIENT is that the use of olmesartan medoxomil against the renin-angiotensin-aldosterone (RAA) system in type 2 DN may attenuate the disease progression and reduce the risk of the composite endpoint of doubling of serum creatinine, ESRD and death in the Japanese and Chinese populations. In their subgroup analysis of the RENAAL study focusing on the Asian subgroup, Chan *et al*. (*18*) demonstrated that losartan significantly reduced the risk of new onset of the primary composite endpoint (risk reduction 35%, $p=0.02$) in the Asian subgroup. These findings have contributed significantly to the overall positive results of the RENAAL study. If the Asian population was removed from the RENAAL study, the results would not have been significant for losartan. In the current worldwide epidemic of diabetes, Asians are expected to become the largest affected population. Given the increased risk of Asian patients for developing ESRD, results from ORIENT will confirm the clinical utility of olmesartan medoxomil in Asian patients with type 2 diabetes.

ACE-Is or ARBs are recommended as first-line drugs in the treatment of hypertension according to the American Diabetes Association (ADA) Position Statement and the Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC 7). ARBs are recommended especially for DN in type 2 diabetes (*21–23*), based on the evidence of large-scale randomized controlled trials in DN. In a recent meta-analysis (*24*) which assessed 43 published randomized controlled trials including a total of 7,545 patients with diabetes, ACE-I treatment was found to significantly reduce the risk of all-cause mortality by about 20% and progression from microalbuminuria to overt proteinuria by about 55%. However, nine trials comparing ACE-I with placebo showed only weak evidence for reduction of risk for progression to ESRD. In addition, most of the studies investigated the effects of these drugs in patients with type 1 diabetes. In contrast, there is strong evidence regarding the use of ARBs in DN, with approximately 22% reduction in risk of ESRD, 51% risk reduction for progression from microalbuminuria to overt proteinuria, and 42% increased chance in regression from microalbuminuria to normoalbuminuria. The meta-analysis included both type 1 and type 2 diabetic patients. Overall, both classes of drugs reduced the risks of onset of DN, increase in proteinuria and progression to ESRD. The clinical trials that investigated the impacts of ACE-I and ARB treatment on outcomes of patients with type 2 diabetes are listed in Table 3.

Strict control of blood glucose and blood pressure is of paramount importance in the treatment of DN. When the protocol for ORIENT was designed in 2002, the recommended target blood pressure according to the hypertension treatment

guidelines in Japan (JSH 2000) (*19*) was <130/85 mmHg. Since then, most guidelines have readjusted the target blood pressure for hypertensive DN patients from <130/85 mmHg to <130/80 mmHg, suggesting stricter blood pressure control. Although based on the UKPDS36 (*25*), the risk associations between blood pressure level and clinical outcomes appeared to be continuous: there were no randomized clinical trial data to show that a target blood pressure <130/80 mmHg conferred superior organ-protective effects compared to blood pressure ≥130/85 mmHg. Besides, in most of the clinical trials on DN, systolic blood pressure was around 140 mmHg at the last visit (Table 3). Olmesartan medoxomil showed similar antihypertensive effects as amlodipine in two clinical trials of essential hypertension. In comparison with other ARBs, olmesartan medoxomil showed the largest decrease in blood pressure. Olmesartan medoxomil also achieved the target blood pressure level of 130/85 mmHg in the highest number of patients in these two studies (*26*, *27*).

In contrast to the RENAAL and IDNT studies, in which none of the patients received ACE-I, patients in ORIENT will be allowed to continue their previously prescribed ACE-I therapy during the study period. Hence, the combination effects of ACE-Is and ARBs can also be evaluated in this study.

Based on their modes of actions, ACE-Is are expected to increase bradykinin levels, reduce AII levels and lower aldosterone levels, while ARBs offer more complete suppression of AII activity *via* the AII type 1 (AT1) receptor, since AII can also be produced by other non-ACE dependent pathways, such as chymase. There is now evidence showing that increased AII activity following treatment with an ARB may enhance the activation of the AII type 2 (AT2) receptors, which are presumed to have vasodilatory, antiproliferative, and antifibrotic activities (*28*). In addition, ARBs may increase bradykinin levels through mechanisms dependent on the stimulation of AT2 receptors (*29*, *30*). Thus, the combination of an ACE-I and ARB may have the additive effects of inhibiting the RAA system and upregulating the bradykinin activity.

A combination therapy with an ACE-I and ARB has been suggested to exert stronger anti-proteinuric effects than either agent used alone (*6*, *31*, *32*). This combination effect of an ACE-I and ARB on proteinuria has been examined in DN patients (*13*, *33–35*). However, thus far, all of the combination studies have only used albuminuria as a surrogate marker rather than using clinical endpoints, such as ESRD. In non-diabetic patients, Nakao *et al*. (*36*) have indicated that combination therapy of an ACE-I and ARB decreased proteinuria and interrupted the progression of nephropathy.

In conclusion, ORIENT aims to investigate the efficacy of olmesartan medoxomil in DN exclusively in Asian type 2 diabetic patients with nephropathy. Results from this study are expected to provide further definitive evidence regarding the optimal treatment strategy in these high-risk patients.

Appendix

ORIENT Study Coordinating Committee: Hirofumi Makino (chair), Sadayoshi Ito, Enyu Imai, Masakazu Haneda, Juliana C. N. Chan.

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